Asymmetric Functionalisation of Prochiral 1,3-Diols Based on an Efficient 1,6-Chiral Induction: the Diastereoselective C–O Bond Fission in Chiral β-Arylsulfinyl Acetal *via* Two Types of Chelation Control

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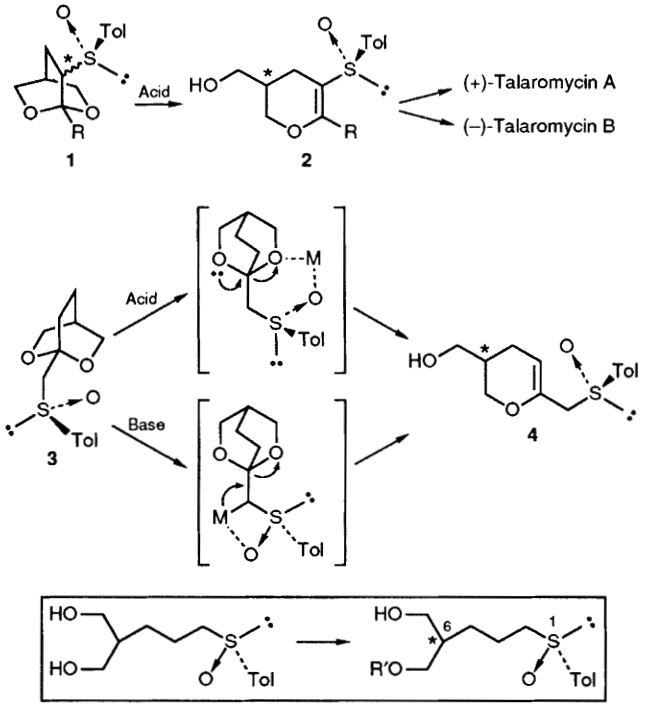
The novel asymmetric functionalisation of a prochiral 1,3-diol is accomplished by the diastereoselective C–O bond fission of the chiral β-arylsulfinyl acetal *via* two types of chelation controlled transition states (**A** and **C** in Scheme 4).

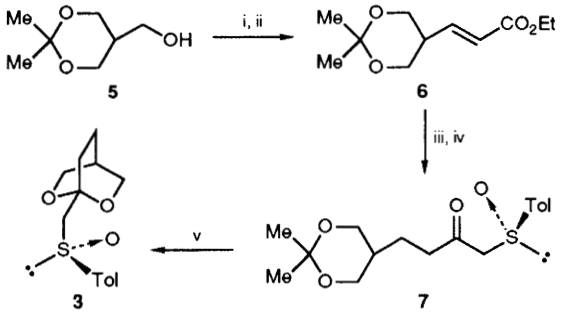
1,3-Diol derivatives are very useful as versatile building blocks in many natural product syntheses.[1] The asymmetric functionalisation of prochiral 1,3-diols is one of the most efficient methods for chiral 1,3-diol construction.[2] While the chirality induction to prochiral 1,3-diols by enzymatic reactions are well known, the approach by chemical methods is rare. Recently, we reported asymmetric functionalisation of prochiral 1,3-diols by the intramolecular acetalisation of the prochiral 1,3-diols with chiral β-keto sulfoxides followed by the diastereoselective C–O bond fission of the acetals under acidic conditions to give the chiral dihydropyran derivatives **2**, which were equivalent to the monoprotected 1,3-diols.[3] We have applied this strategy to the synthesis of (+)-talaromycin A and (−)-talaromycin B (Scheme 1).[4] However, the cleavages of the bicyclic acetal **1** were probably affected by both of the chiral centres. Therefore, we designed the bicyclic acetal **3** in order to accomplish the diastereoselective C–O bond fission controlled only by a sulfinyl chirality. Such a transformation is equivalent to the rare 1,6-chiral induction.

The chiral dioxabicyclo[2.2.2]octane **3**† was prepared from compound **5** in 60% overall yield as shown in Scheme 2.

† Spectroscopic data for compound **3**: $[\alpha]_D^{28}$ + 121 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$): ν_{max}/cm^{-1} 3400, 2970, 2870, 1600, 1490, 1350, 1060, 1030; ^1H NMR (500 MHz, $CHCl_3$): δ 1.86–1.99 (2H, m), 2.03–2.13 (1H, m), 2.32–2.43 (1H, m), 2.40 (3H, s), 2.85 (1H, d, *J* 13 Hz), 3.01 (1H, d, *J* 13 Hz), 4.03 (1H, d, *J* 8 Hz), 4.12 (1H, d, *J* 8 Hz), 4.17 (1H, d, *J* 8 Hz), 4.23 (1H, d, *J* 8 Hz), 7.30 (2H, d, *J* 8 Hz), 7.55 (2H, d, *J* 8 Hz); *m/z*: 266 (M^+); *m/z* 266.0989 (Calc. 266.0977).

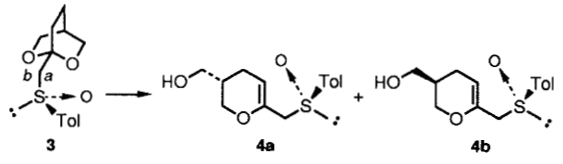


Scheme 1



Scheme 2 *Reagents and conditions*: i, $(COCl)_2$, dimethyl sulfoxide (DMSO), triethylamine, CH_2Cl_2, −60 °C (76%); ii, $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C (84%); iii, H_2, Pd–C, MeOH, room temp. (quant.); iv, Bu^sLi, (*R*)-methyl *p*-tolyl sulfoxide, THF, −78 °C (72%); v, *p*-$MeC_6H_5SO_3H$, H_2O, benzene, room temp. (96%)

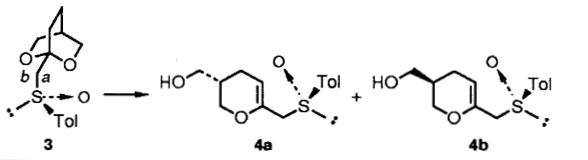
Table 1 The reaction of bicyclic acetal **3** under acidic conditions



Conditions (equiv.)	Yield (%)	Ratio[a] **4a** : **4b**
$TiCl_4$ (10), DME,[b] −50 °C	No reaction	—
$TiCl_4$ (10), DME, −20 °C	83	64 : 36
$TiCl_4$ (10), DME, room temp.	Complex mixture	—
$TiCl_4$ (10), Et_2O, −20 °C	80	53 : 47
$TiCl_4$ (10), THF, −20 °C	81	72 : 28
CF_3CO_2H (10), THF, room temp.	48[c]	1 : 1
$AlCl_3$ (10), THF, room temp.	37	1 : 1

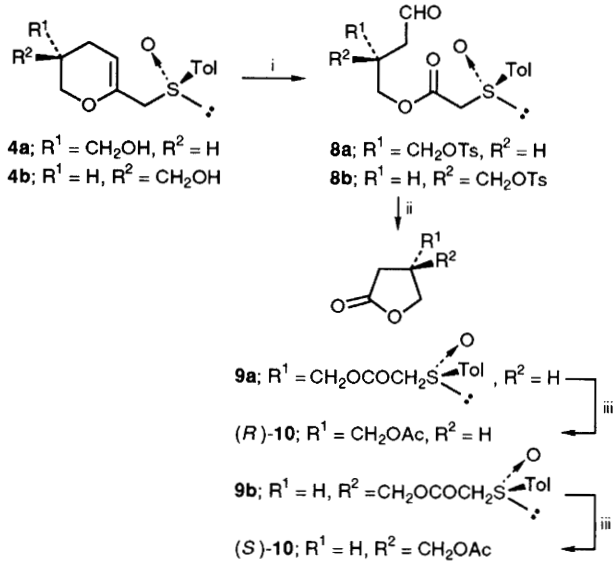
[a] Determined by HPLC as the benzoate unless stated otherwise. [b] DME = 1,2-dimethoxyethane. [c] Isolated as the trifluoroacetate. The ratio was determined by 500 MHz ^1H NMR spectroscopy.

Table 2 The reaction of bicyclic acetal **3** under basic conditions

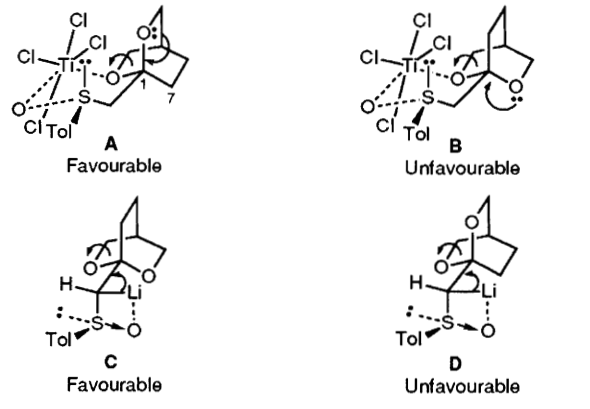


Conditions (equiv.)	Yield (%)	Ratio[a] **4a** : **4b**
LDA (6). THF, −78 °C to room temp.	95	41 : 59
LDA (6), HMPA[b] (6), THF, −78 °C to room temp.	94	33 : 67
LDA (6), 12-crown-4 (6), THF, −78 °C to room temp.	92	28 : 72
LDA (6), DABCO[b] (6), THF, −78 °C to room temp.	81	28 : 72
LDA (6), TMEDA (6), THF, −78 °C to room temp.	92	25 : 75
$LiNEt_2$ (6), THF, −78 °C	91	35 : 65

[a] Determined by HPLC as the benzoate. [b] HMPA = hexamethylphosphorus triamide, DABCO = 1,4-diazabicyclo [2.2.2] octane.



Scheme 3 *Reagents and conditions*: i, *p*-$MeC_6H_4SO_2Cl$, triethylamine, dimethylaminopyridine, CH_2Cl_2, room temp.; O_3, MeOH, −78 °C then Me_2S, room temp. (**8a**: 72%, **8b**: 72%); ii, $NaClO_2$, DMSO, NaH_2PO_4 buffer (**9a**: 96%, **9b**: 96%); iii, Raney Ni, EtOH, room temp. [(*S*)-**10**: quant., (*R*)-**10**: quant.]



Scheme 4

For the regioselective C–O bond cleavage in **3**, various conditions were employed and the results are summarized in Tables 1 and 2. Treatment of **3** with titanium tetrachloride in tetrahydrofuran (THF) at −20 °C resulted in a predominant cleavage at the bond '*a*' yielding mainly **4a**, while under basic conditions [lithium diisopropylamide (LDA), *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), THF, −78 °C to room temp.] The bond '*b*' was cleaved more easily.‡ Other conditions employed were less effective.

The absolute configuration of the products **4a** and **b** was confirmed by their transformation into the known γ-lactone (*R*)-**10** and the enantiomer (*S*)-**10**, respectively as shown in Scheme 3. The compounds **4a** and **b** were separated as *p*-toluenesulfonates by HPLC (column: Waters, RCM 25 × 10, mobile phase : hexane–AcOEt 1 : 1). The *p*-toluenesulfonate (Ts) of **4a** was converted to the aldehyde **8a** by reductive ozonolysis. Treatment of **8a** with sodium chlorite resulted in the formation of γ-lactone **9a** directly. In the reaction, the carboxylate anion generated by the oxidation of the aldehyde attacked the *p*-toluenesulfonate intramolecularly to afford the γ-lactone **9a**. After desulfurisation by Raney Ni, the resulting γ-lactone (*R*)-**10** showed the identical specific rotation with the authentic data. {(*R*)-**10**: $[\alpha]_D^{30}$ −33.0 (*c* 0.68, $CHCl_3$), lit. $[\alpha]_D^{23}$ −33.1 ($CHCl_3$)}. The other *p*-toluenesulfonate **4b** was also converted to (*S*)-**10** {$[\alpha]_D^{23}$ +34.1 (*c* 0.57, $CHCl_3$)} by the same procedure.

We suggest the following reaction mechanism of the acetal cleavage. The bidentate titanium tetrachloride would coordinate between the acetal and the sulfinyl oxygens. The bulky tolyl group would be situated at an equatorial position in a chair-like six-membered transition state (**A** and **B** in Scheme 4). On the other hand, the sulfinyl oxygen would coordinate with the adjacent lithium atom to form a four-membered ring under basic condtions,[6] in which the tolyl group would be *trans* to the bulky bicyclo ring (**C** and **D** in Scheme 4). Since the sulfinyl group tends to locate *anti* to the bulky 7-methylene group rather than the oxygens,§ the transition states **A** and **C** would be more favourable than the transition states **B** and **D**, respectively.¶ Therefore, titanium tetrachloride affords the opposite diastereoselectivity to the amide bases.

In conclusion, we have described a novel method for the asymmetric functionalisation of prochiral 1,3-diols by diastereoselective C–O bond fission of the chiral β-arylsulfinyl acetal. The base promoted acetal cleavage is a new application of the anion neighbouring chiral sulfinyl groups to asymmetric synthesis.

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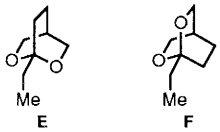
‡ The initially resulting α,β-unsaturated sulfoxide is completely isomerized to the β,γ-unsaturated sulfoxide under these reaction conditions.

§ The result of MM2 calculation in 1-ethyl-2,6-dioxabicyclo[2.2.2]octane shows that conformation **E** is 0.6 kcal mol^{-1} more stable than conformation **F**.



E **F**

¶ The steric repulsion between the 7-methylene group and the *pseudo-axial* chloride attached to the titanium atom also seems to make transition state **B** unstable. Since the monodentate aluminium chloride or trifluoroacetic acid cannot form a cyclic transition state like transition state **A** or **B**, no selectivity is observed.

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